Atty. Docket no. 0208.00063.01R

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPELLANT:	HALE ET AL.	EXAMINER: J.H. ALSTRUM-ACEVEDO
APPLICATION NO.:	10/719,540	ART UNIT: 1616
FILED:	NOVEMBER 20, 2003	CONF. NO.: 3439
FOR:	METHOD FOR TREATING HEADACHE WITH LOXAPINE	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This Appeal Brief is submitted in response to a final Office Action of February 1, 2010, and subsequent to a Notice of Panel Decision from Pre-Appeal Brief Review dated September 2, 2010.

I. REAL PARTY IN INTEREST

The real party in interest is Alexza Pharmaceutical, Inc. The right of Alexza Pharmaceuticals, Inc. to take action in the subject application was established by virtue of the following chain of title:

1. An assignment from the inventors to Alexza Molecular Delivery Corporation , dated November 20, 2003, recorded at Reel/Frame 014747/0304; and

2. A change of name from Alexza Molecular Delivery Corporation to Alexza Pharmaceuticals, Inc., recorded at Reel/Frame 016926/0674.

II. RELATED APPEALS AND INTERFERENCES

The undersigned legal representative of Appellant hereby confirms that there are no known appeals or interferences relating to the present application which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 5-9 and 12-24 are pending in the application. Claims 1, 5-9, 12-20 and 24 are rejected. Claims 21-23 are withdrawn from consideration. Claims 2-4, 10 and 11 have been previously cancelled.

IV. STATUS OF THE AMENDMENTS

No claim amendments were submitted in response to the final Office Action of February 1, 2010. No amendments remain outstanding.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention relates generally to a method of treating headache comprising administering an effective amount of loxapine, pharmaceutically acceptable salts of loxapine or a loxapine prodrug at a dose of 0.3 to 6.0 mg. In the alternative, the amount of loxapine salt or prodrug administered is sufficient to produce a blood concentration of loxapine equivalent to the administration of about 0.3 to about 6.0 mg of loxapine. Independent claims 1 and 24 find support in the specification at page 4, lines 25-28 ([0014]); page 5, lines 7-30 ([0016] – [0017]); page 7, lines 3-11 ([0022]) and lines 31-33 ([0025]); Example 1, page 16, line 2 to page 17, line 7 ([0051] – [0053]); and Example 4, page 23, line 9 to page 24, line 20 ([0090) – [0092]).

VI. GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

Claims 1, 5-9, 12-15 and 24 are rejected under Section 103(a) over Burns et al., U.S. 5,284,133, and Drug Information Handbook, 2nd ed. (Lexi-Comp, Inc., Cleveland, 1994-5, pp. 554-555).

Claims 16-17 and 19-20 are rejected under Section 103(a) over Burns et al., DIH as applied to claims 1, 5-9, 12-15 and 24, further in view of Nguyen et al., U.S. 7,040,314.

Claims 16-18 are rejected under Section 103(a) over Burns et al. and DIH as applied to claims 1, 5-9, 12-15 and 24, and further in view of Rabinowitz et al., US 2004/0009128.

Claims 1, 16-17 and 19 are rejected under the doctrine of obviousness-type double patent over claims 7, 9, 10, 12 and 13 of U.S. Pat. No. 6,716,416. Appellants have previously indicated that they will file a terminal disclaimer over this prior patent upon indication of allowable subject matter and affirm here their intention to do so.

Claims 1 and 16-20 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 12, 15, 16 and 18 of copending USSN 10/633,876, now U.S. Pat. No. 7,645,442. Claims 1 and 16-20 are also provisionally rejected over claims 1 and 7-9 of USSN 10/633,877, now U.S. Pat. No. 7,585,493. Appellants have previously indicated that they will file terminal disclaimers over these copending applications (now issued patents) upon indication of allowable subject matter and affirm here their intention to do so.

Claims 1 and 5-15 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 1 and 15 of USSN 11/346,548. Appellants respectfully point out that this patent application is now abandoned, thereby rendering the provisional rejection moot.

Because the foregoing obviousness-type double patenting rejections are not the subject of the current appeal, they will not be further discussed herein.

VII. ARGUMENT

A. Summary of the Argument Relating to Claims 1, 5-9, 12-15, 16-18, 19-20 and 24

Appellants present arguments that establish that *prima facie* obviousness has not been established for claims 1, 5-9, 12-15 and 24. Appellants next demonstrate that even if *prima facie* obviousness were established, it would be rebutted by the evidence of unexpectedly improved results set forth in the specification. Claims 16-18 and 19-20 are likewise patentable by virtue of their dependency on claims 1, 5-9, 12-15 and 24.

B. Argument in Support of Claims 1, 5-9, 12-15 and 24 and Claims Dependent Thereon

Claims 1, 5-9, 12-15 and 24 are rejected under Section 103(a) over Burns et al., U.S. 5,284,133, and Drug Information Handbook, 2nd ed. (Lexi-Comp, Inc., Cleveland, 1994-5, pp. 554-555). The Examiner's position is that the two cited references establish *prima facie* obviousness of the claims.

It is respectfully submitted that *prima facie* obviousness has not been established. It is settled law that *prima facie* obviousness requires that the cited references teach or suggest all of the elements recited in the rejected claim (*In re Royka*, 180 USPQ 580 (CCPA 1974); and *In re Boe and Duke*, 184 USPQ 38 (CCPA 1974)). Claims 1 and 24 both recite that the method of treating a headache comprises administration of loxapine, or one of its salts or prodrugs, at 0.3 to 6.0 mg to the patient. None of the cited references teach the element of treating headache with loxapine. They also do not teach or suggest a loxapine dosage of 0.3 to 6.0 mg.

Burns et al., US 5,284,133, teach an improved method for inhalation administration of a long list of drugs, using an inhalation device that monitors and enforces the time and amount of inhalation by the patient. It is submitted that Burns et al. does not teach or suggest that loxapine is useful in treating headache. Turning to the passage cited by the Examiner which is in dispute (col. 7, lines 3-30):

> As delivering systemic drugs by aerosol administration gains wider acceptance, there will be increased demands on the safety of inhalation devices. As is established by [citation omitted], patient compliance with nebulizers and MDIs is not very good and many patients are not truthful about their drug usage. It is expected that with some drugs, relying on proper patient aerosol administration will not be acceptable. For example, with neuroleptics, psychotropics, narcotic antagonists, other central nervous system

> (CNS) drugs and headache analgesics, such as proclorperazine, fluphenzine [sic, fluphenazine] hydrochloride, chlorpromazine, trifluperazine [sic, trifluoperazine] hydrochloride, thioridizine hydrochloride, **loxapine hydrochloride**, and haloperidol decanoate, . . . and migraine headache analgesics such as various butalbitol combinations, propanolol and nifedipine, there may be a tendency of some patients to overdose themselves.

The list of pharmaceuticals, "prochlorperazine, fluphenazine hydrochloride, chlorpromazine, trifluoperazine hydrochloride, thioridizine hydrochloride, loxapine hydrochloride, and haloperidol decanoate," refers to "first generation" or "typical" antipsychotics, as was known to the skilled artisan at the filing date of the subject application (see US Pat. No. 6,150,353, submitted with the IDS of July 30, 2008). In Kelly, A. (2000) "Migraine: Pharmacotherapy in the Emergency Department" WJM 173:189-193 (submitted with IDS of July 30, 2008), prochlorperazine and chlorpromazine were determine to have greater than 70% efficacy in treating headaches, while haloperidol required additional study to determine whether it might be useful. In Bowden (1988) Clin. Exp. Pharmacol. 15:457-463 (submitted with IDS of July 30, 2008), trifluoperazine was reported to be effective in relief of asthma (no mention was made of headache treatment). Thus, based on the art previously submitted by Appellants, it is respectfully submitted that the list of pharmaceuticals in the disputed passage were known to be antipsychotics (neuroleptics) and may have had other applications. At least one (haloperidol) did not seem to be useful in treatment of headache. Nothing in the disputed passage of Burns et al. points to all of "prochlorperazine, fluphenazine hydrochloride, chlorpromazine, trifluoperazine hydrochloride, thioridizine hydrochloride, loxapine hydrochloride, and haloperidol decanoate" as being headache analgesics. Given the wording of the passage, each of "prochlorperazine, fluphenazine hydrochloride, chlorpromazine, trifluoperazine hydrochloride, thioridizine hydrochloride, loxapine hydrochloride, and haloperidol decanoate" could have been ncuroleptics, psychotropics, narcotic antagonists, or other CNS drugs.

In this context, the skilled artisan would reasonably interpret each of the listed drugs as "typical antipsychotics" and not as a revelation that all or some or all of the listed drugs are also useful as headache analgesics. Given the failure to teach loxapine as a headache analgesic, it is submitted that *prima* facie obviousness has not been established.

The foregoing conclusion would have been further supported by the teaching in Burns et al. of "migraine headache analgesics such as various butalbitol combinations, propanolol and nifedipine," which clearly indicates that migraine headache analgesics do not include loxapine. At the very least, this teaching supports the non-obviousness of claim 5.

The other element of claims 1 and 24 that is not taught by the cited references is a dosage of 0.3 to 6.0 mg. The Drug Information Handbook, 2nd edition, teaches an oral dose of "10 mg twice daily, increase dose until psychotic symptoms are controlled; usual dose range: 60-100 mg/day in divided doses 2-4 times/day." Intramuscular dose is 12.5-50 every 4-6 hours or longer as needed." There is nothing in these ranges or elsewhere in the reference that teaches or suggests the 0.3 to 6.0 mg recited in subject claims 1 and 24.

It is argued in the final Office Action that it would be a matter of routine optimization for the skilled artisan to obtain the claimed dosage range. Appellants respectfully disagree. Appellants respectfully direct the Examiner's attention to the claimed dosage range, which is 0.3 to 6.0 mg, not 0.3 to 20 mg as stated by the Examiner on page 3, third paragraph, of the Office Action. Neither DIH nor Burns et al. teach or suggest use of loxapine or optimization of its antipsychotic dose for treatment of headache. In fact, DIH teaches increasing dose (away from the claimed range) until psychotic symptoms is controlled. There would be no opportunity in the course of increasing the dose above 10 mg twice daily to control psychosis, to note that a lower dose of 0.3-6.0 mg results in headache abatement. If anything, DIH teaches away from routine optimization to obtain the recited lower dose.

For the foregoing reasons, it is respectfully submitted that claims 1, 5-9, 12-15 and 24 are not obvious over Burns et al. and Drug Information Handbook, and withdrawal of the rejection is requested.

Claims 16-17 and 19-20 are rejected under Section 103(a) over Burns et al. and DIH as applied to claims 1, 5-9, 12-15 and 24, further in view of Nguyen et al., U.S. 7,040,314.

Appellants respectfully submit that Burns et al., DIH and Nguyen et al. do not establish *prima facie* obviousness of claims 1, 5-9, 12-15, 16-17, 19-20 and 24 because they do not teach or suggest all of the elements of claims 1 and 24 or of any of the claims dependent thereon. As discussed above, it is established law that failure of the cited references to teach or suggest all of

the elements recited in the claims, constitutes a failure to establish *prima facie* obviousness (*In re Royka*, *supra*; and *In re Boe and Duke*, *supra*).

As argued by Appellants above, Burns et al. and DIH do not teach all of the elements of claims 1, 5-9, 12-15 and 24, because they do not teach the two elements of a method of treating a headache comprising administration of loxapine, or one of its salts or prodrugs, using a dosage of 0.3 to 6.0 mg. Nguyen et al. do nothing to cure the deficiencies of Burns et al. and DIH.

Nguyen et al. describe a device for delivery of a liquid aerosol formulation that includes a high volatility carrier and a drug. The drug can be an analgesic, antipsychotic, anxiolytic, drug for migraine headaches, among many others. Each of the drug categories contains a list of many possible drugs. Neither analgesics nor migraine drugs list loxapine as a member of their categories. Loxapine is listed only in the category of anxiolytics. Thus, Nguyen et al. do not teach or suggest loxapine as being useful in the treatment of headache.

Nguyen et al. also do not teach or suggest any dose for loxapine, and therefore do not supply the element of a dose of 0.3-6.0 mg loxapine. On these bases, it is submitted that Nguyen et al. do not cure the deficiencies of Burns et al. and DIH.

Claims 16-18 are rejected under Section 103(a) over Burns et al. and DIH as applied to claims 1, 5-9, 12-15 and 24, and further in view of Rabinowitz et al., US 2004/0009128.

Appellants respectfully submit that Burns et al., DIH and Rabinowitz et al. do not establish *prima facie* obviousness of claims 1, 5-9, 12-15 and 16-18 and 24 because they do not teach or suggest all of the elements of claims 1 and 24 or of any of the claims dependent thereon. As discussed above, it is established law that if the cited references do not teach or suggest all of the elements recited in the claims, then *prima facie* obviousness is not established (*In re Royka*, *supra*; and *In re Boe and Duke*, *supra*).

Rabinowitz et al. describe delivery of drug amine aerosols via an inhalation device. The method involves heating a coating of the drug amine on a substrate to generate the vapor and drawing air through the device, condensing the vapor to form aerosol particles containing less than 10% degradation products. The drug amines can include antipsychotics and analgesics among others. However, neither of these drug categories includes loxapine. Another drug amine

is anxiolytics which can include loxapine. However, Rabinowitz et al. do not teach or suggest the element of using loxapine to treat headaches.

Rabinowitz et al. also do not teach or suggest any dosage for loxapine and do not teach the specific dose of 0.3-6.0 mg loxapine. On the bases of the foregoing it is respectfully suggested that Rabinowitz et al. do not cure the deficiencies of Burns et al. and DIH.

Appellants further submit that even if *prima facie* obviousness had been established, it is rebutted by evidence of unexpectedly improved results (*In re Dillon*, 16 USPQ2d 1897, 1901 ((Fed. Cir. 1990); *cert. denied*, 500 US 904 (1991)). As stated on page 4, paragraph [0014], of the subject as-filed application, loxapine has not previously been found to be effective in treatment or control of pain, and the subject invention establishes that it is, in fact, "surprisingly effective" in such treatment or control.

Example 1 illustrates that loxapine is effective at reducing writhing in a mouse acetic acid model at doses as low as 0.125 to 2.0 mg/kg. Additionally, Example 4 illustrates that doses of 5 and 10 mg are rapidly effective in the treatment of migraine in humans, and doses as low as 1.25 or 2.5 mg are also effective in treatment of migraines (though the pain relief is not as rapid). These experimental results clearly support the claimed range of 0.3 to 6.0 mg which is literally supported in paragraph [0025] of the as-filed application.

These results demonstrating unexpectedly improved results within the claimed range, effectively rebut any case of *prima facie* obviousness. Withdrawal of the Section 103(a) rejection of claims 1 and 24 which recite the 0.3 to 6.0 mg dose is respectfully requested.

VIII. APPENDIX OF CLAIMS

1. (Previously Presented) A method for treating headache comprising administering to a subject in need of headache relief, an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine, and prodrugs of loxapine wherein 0.3 to 6.0 mg of loxapine is administered, or an amount of a salt or prodrug of loxapine is administered that produces in the subject a blood concentration of loxapine equivalent to the administration of 0.3 to about 6.0 mg of loxapine.

2-4. (Cancelled)

5. (Previously Presented) A method in accordance with claim 1, wherein said headache is a migraine headache.

6. (Previously Presented) A method in accordance with claim 1, wherein said headache is a cluster headache.

7. (Previously Presented) A method in accordance with claim 1, wherein said headache is a tension-type headache.

8. (Previously Presented) A method in accordance with claim 1, wherein said compound is administered by inhalation.

9. (Previously Presented) A method in accordance with claim 1, wherein said subject is human, said headache is a migraine headache, and said compound is administered by inhalation.

10. (Cancelled)

11. (Cancelled)

12. (Previously Presented) A method in accordance with claim 1, wherein the compound is formulated so as to result in a maximum blood level of loxapine within about 30 minutes from administration.

13. (Previously Presented) A method in accordance with claim 1, wherein the compound is formulated so as to result in a maximum blood level of loxapine within about 15 minutes from administration.

14. (Previously Presented) A method in accordance with claim 1, wherein the compound is formulated so as to result in a peak rate of increase in the blood level of loxapine of at least about 1 ng/ml/minute.

15. (Previously Presented) A method in accordance with claim 1, wherein the compound is formulated so as to result in a blood level of loxapine of at least about 5 ng/ml within about 15 minutes from administration.

16. (Previously Presented) A method in accordance with claim 1, wherein said compound is administered via inhalation using a rapid-heating drug delivery article or a thin-film drug delivery article.

17. (Previously Presented) A method in accordance with claim 1, wherein said compound is administered via an inhalation delivery device, wherein said compound is vaporized and condensed to provide at least 50% recovery of said compound in an aerosol, and wherein said aerosol contains less than about 5% by weight of compound degradation products.

18. (Previously Presented) A method in accordance with claim 17, wherein said compound is coated on a substrate in the delivery device as a film having a thickness between about 0.5 and 20 μm.

19. (Previously Presented) A method in accordance with claim 1, wherein said compound is administered in the form of an aerosol having a mass median aerodynamic diameter of between about 0.01 and about 3 μm.

20. (Previously Presented) A method in accordance with claim 1, wherein said compound is administered via a rapid heating drug delivery article, and wherein said compound is volatized from a compound composition film under conditions sufficient to provide an aerosol having at least 50% recovery of said compound and containing less than about 10% by weight of compound degradation products.

21. (Withdrawn) A composition for the treatment of headache, said composition comprising (a) an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts thereof, and prodrugs thereof, and (b) a pharmaceutically acceptable carrier.

22. (Withdrawn) A composition of claim 21, further comprising one or more analgesic, anti-inflammatory or antimigraine agents.

23. (Withdrawn) A thin-film composition for the treatment of headache comprising an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts thereof and prodrugs thereof, and having a film thickness of from about 0.5 to about 20 μm.

24. (Previously Presented) A method for treating headache pain in a subject comprising administering to said subject an effective amount of a compound selected from the group consisting of loxapine, pharmaceutically acceptable salts of loxapine and prodrugs of loxapine wherein 0.3 to 6.0 mg of loxapine is administered, or an amount of a salt or prodrug of loxapine is administered that produces in the subject a blood concentration of loxapine equivalent to the administration of 0.3 to about 6.0 mg of loxapine.

IX. APPENDIX OF EVIDENCE

Appended hereto are copies of the following authorities and case law:

In re Royka, 180 USPQ 580 (CCPA 1974);

In re Boe and Duke, 184 USPQ 38 (CCPA 1974);

In re Dillon, 16 USPQ2d 1897, 1901 ((Fed. Cir. 1990); cert. denied, 500 US 904 (1991);

US Pat. No. 6,150,353, submitted with the IDS of July 30, 2008;

Kelly, A. (2000) "Migraine: Pharmacotherapy in the Emergency Department" WJM 173:189-193, submitted with IDS of July 30, 2008; and

Bowden (1988) Clin. Exp. Pharmacol. 15:457-463, (submitted with IDS of July 30, 2008.

X. RELATED PROCEEDINGS APPENDIX

As discussed above, there are no related proceedings.

XI. CLOSING REMARKS

Submitted herewith is a Petition for a two-month Extension of Time with the authorization to charge the necessary fee to Deposit Account 19-5117. This constitutes a request for any additional needed extension of time and an authorization to charge all fees therefor to Deposit Account No. 19-5117, if not otherwise requested. Appellants also authorize the charge of $270 under 37 CFR § 41.20(b)(2) and any deficiency therein to Deposit Account No. 19-5117.

Respectfully submitted,

Date: December 1, 2010

/Margaret M. Wall/

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